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The Effect of Trihalomethane and Haloacetic Acid Exposure on Fetal Growth in a Maryland County

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As water flows from treatment plants to the tap, chlorine, used to disinfect surface water meant for residential use, reacts with residual organic and inorganic matter, creating chlorine disinfection by-products. In recent years, these by-products have been scrutinized as a potential reproductive and developmental hazard. This study examined whether exposure to the four total trihalomethanes or the five haloacetic acids (two major subgroups of chlorine disinfection by-products) was related to an increased risk of intrauterine growth retardation in four regions of a Maryland county from 1998 to 2002. Maternal exposure to each by-product was evaluated for each trimester as well as over the entire pregnancy. The authors were not able to demonstrate any consistent, statistically significant effect on intrauterine growth retardation associated with any of the chlorine disinfection by-products, nor did they find any indication of a dose-response relation. However, they did find some potential for a slightly elevated risk of intrauterine growth retardation during the second and third trimesters for both total trihalomethanes and five haloacetic acids when comparing increasing quintiles of exposure to constituents of total trihalomethanes and five haloacetic acids.

chlorine; disinfectants; fetal growth retardation; trihalomethanes; water supply

Abbreviations: CDBPs, chlorine disinfection by-products; CI, confidence interval; HAA5, five haloacetic acids; IUGR, intrauterine growth retardation; OR, odds ratio; TTHM, total trihalomethane.

Since the early 1900s, chlorine, a water-soluble disinfectant, has been used in the treatment of drinking water to decrease the incidence of waterborne infectious diseases, significantly reducing morbidity and mortality in the United States (1). Its use results in the formation of chlorine disinfection by-products (CDBPs), high levels of which have recently been suggested to cause numerous adverse health outcomes (2).

In the 1980s and 1990s, CDBPs were investigated because of increased concerns that they may be carcinogenic. Cohort and case-control studies evaluated cancers of the bladder, colon, pancreas, and kidney (3, 4). In 1991, 1999, and again in 2004, the International Agency for Research on Cancer evaluated the evidence of the human carcinogenicity of chlorinated water as well as the by-products it produces (5). Although the extent of the data provided the International Agency for Research on Cancer with insufficient evidence to classify the by-products as carcinogenic, the research served as an impetus for the US Environmental Protection Agency to establish maximum contaminant level goals for several of the by-products, including total trihalomethane (TTHM) and five haloacetic acids (HAA5) (6).

In recent years, CDBPs have also been scrutinized as potential teratogens. Toxicology studies evaluating the relation between TTHM exposure and intrauterine growth retardation (IUGR) have shown significant fetotoxicity, including decreased fetal body weight and fetal crown-rump length in mice (7), rats (8–10), and rabbits (10).

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Additionally, both dichloroacetic acid and trichloroacetic acid have been shown to be teratogenic in rats and mice (11). However, these studies evaluated acute exposures at levels far greater than expected for human exposure, likely causing maternal toxicity, which in turn could adversely affect fetal development (12). It is unclear whether retarded fetal development is evident with no apparent maternal toxicity.

Five major reviews have evaluated the epidemiologic evidence for adverse birth outcomes related to TTHM exposure (12–16). Each concluded that, while there appears to be suggestive evidence associating elevated TTHM levels with adverse reproductive outcomes, current evidence fails to support a dose-response model. Overall, a weak positive association is noted between IUGR and prenatal TTHM exposure in a total of six studies, four showing a statistically significant positive association (17–22).

Weaknesses in the assessment of TTHM exposure also limit the interpretation of epidemiologic results. For example, Kramer et al. (20) report an increased risk of IUGR in women residing in regions with high chloroform (odds ratio (OR) = 1.8, 95 percent confidence interval (CI): 1.1, 2.9) and dichlorobromomethane (OR = 1.7, 95 percent CI: 0.9, 2.9) levels in the water. However, these TTHM levels were assessed during a regional drought and were then extrapolated to the corresponding study population the following year. Seasonal variation in water levels has been shown to correlate with TTHM concentrations (23), which may significantly bias these estimates. Seasonal fluctuation in TTHM levels is of concern in studies measuring TTHM quarterly or annually and then ''averaging'' the results to biweekly concentrations to estimate either trimester-specific or entire pregnancy exposure levels (18, 19, 21, 22). Additionally, few epidemiologic studies have evaluated the effects of other CDBPs such as the HAA5 or haloacetic nitriles.

The objective of this study was to determine whether increased TTHM or HAA5 levels in residential water were associated with an increased risk of IUGR, defined as affecting infants who are small for gestational age, in four regions of a Maryland county during 1998–2002.

MATERIALS AND METHODS

Population

Monthly measurements of TTHM for four sampling points in a Maryland county were obtained from the local water utility company for 1997–2002. Monthly measurements of HAA5 were obtained for 1999–2002 only, when the water utility began consistently tracking HAA5 levels. The sampling points represented varying distances from the water treatment facility. Measurements included specific values for the four trihalomethanes (bromoform, chloroform, bromodichloromethane, and dibromochloromethane) and five of the haloacetic acids (chloroacetic acid, dichloroacetic acid, trichloroacetic acid, bromoacetic acid, and dibromoacetic acid). Average TTHM and HAA5 levels were calculated by summing the constituents.

Birth certificate data for the Maryland county, for which individual identifying information was removed, were obtained from the Maryland State Department of Health and Mental Hygiene, Office of Vital Records for 1998–2002. Data for only those mothers whose residences were located in zip codes corresponding to the water utility's point measurements were used in the analysis. Multiple zip codes per region were selected when they were in the same water pressure zone and were served by the same water utility. The analysis was restricted to singleton livebirths in which the infants were classified as African American, Caucasian, or Hispanic American. Additionally, information on infants born after less than 25 weeks or more than 42 weeks of gestation was excluded from analysis because there are no known standards for the outcome of interest in this population.

Exposure assessment

The primary exposure variables, average gestational TTHM and HAA5 levels, were computed from averaged biweekly TTHM and HAA5 measurements for the particular region based on the delivery date and estimated gestational period for each pregnancy. TTHM exposure for infants born in the first three quarters of 1998 was determined by using water sampling measures from 1997. Similarly, infants born prior to the last quarter of 1999 were excluded from the HAA5 analysis because of our inability to assess exposure throughout the pregnancy. Trimester-specific TTHM and HAA5 levels were also calculated for each pregnancy.

Outcome

The primary outcome variable, IUGR, is a measure commonly used to determine fetal growth retardation (18, 19, 21). It was defined as affecting an infant whose birth weight was below the 10th percentile for gestational age (adjusted for sex and race) by using standards compiled from US Census data (24, 25).

Potential confounders

Demographic variables available in the vital records and known to be associated with the primary outcome were evaluated, including mother's age, maternal weight gain, race/ethnicity of the child, adequacy of prenatal care (determined by the Kessner Index) (26), marital status, tobacco/cigarette use, and alcohol consumption. Not all possible confounders (specifically socioeconomic factors) could be evaluated given our dependency on data obtained from vital records. However, maternal residence was evaluated to determine whether region was an independent predictor of the outcome by evaluating the association between mother's residence in one of the four regions and IUGR.

Analysis

The association between IUGR and the primary exposure variable and confounders was explored by univariate

methods. Continuous variables were analyzed by using Student's t test and categorical variables by the Mantel-Haenszel chi-square test. To evaluate the linearity assumption for continuous variables (e.g., mother's age) to be included in the model, ordered levels of continuous variables were created and plotted against the log odds of IUGR for each ordered level. Variables failing to demonstrate a linear relation were appropriately categorized. Risk factors for fetal growth restriction have been reported extensively elsewhere (27) and are not the subject of this paper, except to allow for appropriate control of covariates in this analysis.

A logistic regression model was used to evaluate the relation between exposure to TTHM or HAA5 and IUGR while adjusting for potential confounders. In addition to averaged TTHM and HAA5 levels, each of the component CDBPs was evaluated separately as a primary exposure variable. Predictor variables whose univariate test showed a p value of <0.25 in relation to the outcome were included in the regression model. By using an iterative forward stepwise approach, we added variables one at a time to determine how they affected the model (using the maximum-likelihood estimation technique). The following predictor variables were found to be significantly associated with the outcome variable and were subsequently included in all logistic regression models: marital status, mother's age dichotomized into two nominal variables (teen and >35 years), Kessner Index, and tobacco use.

TTHM and HAA5 exposure were initially assessed as continuous variables. Since no linear association was evident, the exposure variables were divided into quintiles and were evaluated as both ordinal variables and nominal variables to assess for trends associated with the primary outcome. Upper quintiles were compared with lower quintiles to further evaluate the possible effects of differential exposure.

Additional analyses exploring current Environmental Protection Agency–recommended thresholds for TTHM and potential thresholds of other CDBP constituents were performed by comparing high with low exposure levels of CDBPs for trimester-specific and total gestational exposures, using increasing cutpoints to define "high-level exposure." For CDBPs regulated by the Environmental Protection Agency, we used the established Maximum Contaminant Level Goal as cutpoints, defining cutpoints starting with the median level and increasing them incrementally. For CDBPs not regulated by the Environmental Protection Agency, we started at the median value and increased the cutpoints incrementally.

A correlation analysis of main-effect exposures was performed by using the standard correlation.

For models appearing to show the strongest effect for the primary exposure, population attributable fractions for the CDBP and other predictor variables were computed from the logistic regression model, and confidence intervals were calculated based on asymptotic approximations (28).

Statistical analyses were conducting by using SAS version 8.1 for Windows (SAS Institute, Inc., Cary, North Carolina) and Stata version 8 (Stata Corporation, College Park, Texas) software. Two-tailed statistical significance was evaluated by using a p value of 0.05.

RESULTS

There were 18,800 births in the four regions of the Maryland county from 1998 to 2002. A total of 713 were excluded from analysis because they were not singleton births. For 15,416 of the remaining 18,087 births, the child's race/ethnicity was recorded as African American, Caucasian, or Hispanic American. An additional 101 births were excluded because the infant's gestational age was not 25–42 weeks, leaving a total study population of 15,315 for analysis. Table 1 shows the demographics of the included study population by region. The ethnicity of infants born in regions 1 and 2 was similar, with approximately 15 percent of the population classified as Caucasian. Regions 3 and 4 were more diverse, with approximately a third of the included births in each of the ethnic categories.

In univariate analysis, any tobacco use during pregnancy (OR = 1.89, 95 percent CI: 1.44, 2.49), lack of adequate prenatal care (OR = 1.37, 95 percent CI: 1.20, 1.56), and having an unmarried (OR = 1.43, 95 percent CI: 1.26, 1.63) or teenage (OR = 1.54, 95 percent CI: 1.25, 1.91) mother were all found to be independently associated with an increased risk of IUGR. Maternal residence in one of the four geographic regions was not associated with IUGR ($p = 0.9$). Alcohol consumption during pregnancy (yes/no) was not associated with an increased risk of IUGR (OR = 1.24, 95 percent CI: 0.69, 2.26).

As noted elsewhere (29), there was seasonal fluctuation in the levels of both TTHM and HAA5, which were higher during the summer months (figures 1 and 2). This finding was similar in each of the four regions (data not shown). While collinear, there were differences between component TTHM and HAA5. Mean CDBP exposure levels were similar during each trimester for each of the four regions (table 2), with trimester-specific exposure levels varying from 14 ppb to 179 ppb for TTHM and from 27 ppb to 64 ppb for HAA5.

Since there was no apparent linear relation between CDBP exposure and the log odds of IUGR, exposure levels for each of the TTHM and HAA5 constituents were divided into quintiles for each trimester and for the entire pregnancy. Each CDBP was modeled to assess its relation to the outcome by comparing increasing quintile levels (tables 3 and 4).

Analyses for both TTHM and HAA5 seemed to indicate an increased risk of IUGR (nonsignificant for TTHM, significant for most quintiles of HAA5) during third-trimester exposure for exposures at the second quintile and above. However, this finding was not evident when the constituent exposures were analyzed (with the exception of dichloroacetic acid and trichloroacetic acid). In addition, there did not appear to be an increased risk of IUGR with increasing quintiles of either the constituent or the summary TTHM or HAA5 (dose response).

In an effort to further evaluate for an effect, we compared the upper two quintiles (4 and 5) with the lowest two quintiles (1 and 2) for TTHM, HAA5, and all constituents. The results showed a slight, nonsignificant increased risk of IUGR for all constituent CDBPs except chloroform and trichloroacetic acid during the second trimester, and a similar slight, nonsignificant increased risk for all CDBPs except

TABLE 1. Demographics for singleton births in four regions of a Maryland county, 1998–2002

	Region 1 ($n = 1,780$)		Region 2 ($n = 749$)		Region 3 ($n = 6,010$)		Region 4 ($n = 6,776$)		Total ($n = 15,315$)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Gender										
Male	906	50.9	371	49.5	2,998	49.9	3,382	49.9	7,657	50.0
Female	874	49.1	378	50.5	3,012	50.1	3,394	50.1	7,658	50.0
Race/ethnicity										
African American	140	7.9	57	7.6	1,595	26.5	2,044	30.2	3,836	25.1
Caucasian	1,549	87.0	630	84.1	2,375	39.5	2,143	31.6	6,697	43.7
Hispanic American	91	5.1	62	8.3	2,040	33.9	2,598	38.2	4,782	31.2
Teenage mother	16	0.9	43	5.7	445	7.4	498	7.4	1,002	6.5
Mother aged >35 years	608	34.2	137	18.3	955	15.9	1,155	17.1	2,855	18.6
Tobacco use during pregnancy	9	0.5	55	7.3	238	4.0	181	2.7	483	3.2
Alcohol consumption during pregnancy	17	1.0	4	0.5	50	0.8	64	1.0	135	1.0
Marital status										
Single	79	4.4	131	17.5	1,784	29.7	2,074	30.6	4,068	26.6
Married	1,701	95.6	618	82.5	4,226	70.3	4,702	69.4	11,247	73.4
Adequacy of prenatal care*										
Adequate	1,466	82.3	598	79.8	4,214	70.1	4,987	73.6	11,265	73.6
Intermediate	304	17.1	144	19.2	1,725	28.7	1,730	25.5	3,903	25.5
Inadequate	10	0.6	7	0.9	71	1.2	59	0.9	147	1.0
	Mean	95% CI†	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Mother's age (years)	33.7	33.5, 33.9	30.0	29.5, 30.4	29.0	28.9, 29.2	29.1	29.0, 29.3	29.6	29.5, 29.7
Maternal weight gain (pounds‡)§	30.6	30.1, 31.1	30.7	29.8, 31.6	29.5	29.2, 29.8	29.8	29.5, 30.1	29.8	29.6, 30.0
Gestational age (weeks)	38.8	38.8, 38.9	38.9	38.8, 39.0	38.8	38.8, 38.9	38.7	38.7, 38.8	38.8	38.8, 38.8
	No.	%	No.	%	No.	%	No.	%	No.	%
IUGR†	126	7.1	50	6.7	441	7.3	497	7.3	1,114	7.3

* Determined by the Kessner Index.

† CI, confidence interval; IUGR, intrauterine growth retardation.

‡ One pound = 0.454 kg.

§ A total of 111 observations were recorded as 0 (region 1: $n = 9$; region 2: $n = 3$; region 3: $n = 48$; and region 4: $n = 51$). One observation in region 3 was coded as 99 and was excluded from the analysis.

dibromochloromethane and bromodichloromethane in the third trimester.

No significant increases in risk were found in our threshold analysis comparing high with low TTHM exposure levels. However, we did find a pattern of elevated risk (adjusted ORs = >1.10) for TTHM at cutpoints above 70 ppb for third-trimester exposure (table 5). The pattern varied for the trihalomethane constituents, with chloroform demonstrating a nonsignificant increasing risk with increasing cutpoints (ranging from >35 ppb to >50 ppb) in the third trimester, bromoform appearing to show a pattern of elevated risk at third-trimester levels of more than 0.35 ppb, and dibromochloromethane appearing to indicate a consistent elevated risk at third-trimester levels of more than 5 ppb. No patterns of threshold or dose response were seen for exposure to total haloacetic acids, but, for the constituents, there seemed to be a pattern of elevated risk at third-trimester levels, with levels of more than 0.7 ppb for bromoacetic acid and more than 0.8 ppb for dibromoacetic acid. For dichloroacetic acid, there was a statistically significant increased third-trimester risk (ORs = 1.23) with cutpoints at 14–15 ppb, but not for higher cutpoints.

We found little to no correlation between overall exposure levels of trihalomethanes and haloacetic acids, nor

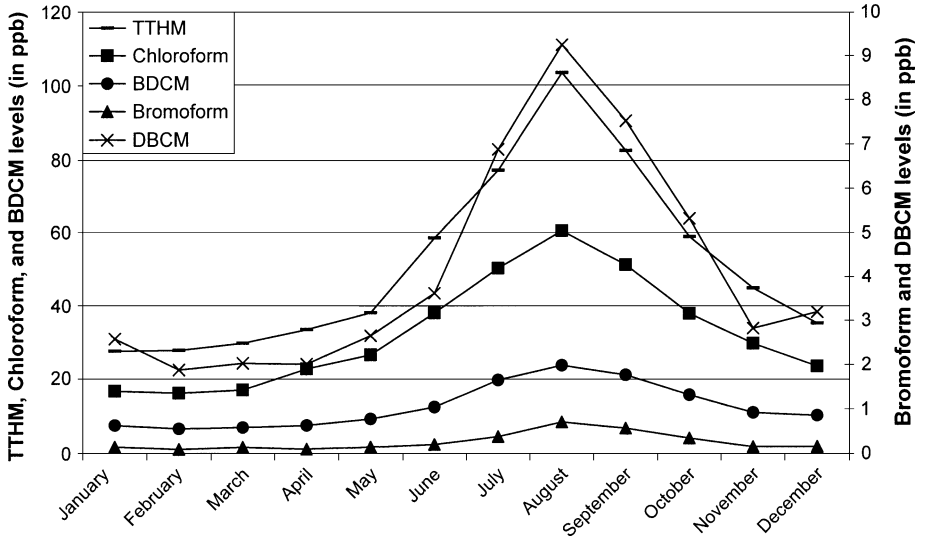

FIGURE 1. Seasonal fluctuation in total trihalomethane (TTHM) levels in four regions of a Maryland county, 1997–2002. BDCM, bromodichloromethane; DBCM, dibromochloromethane.

individual constituent levels between trimesters. We also evaluated the correlation of CDBP exposure levels in which there was a significant or nonsignificant effect. We found a correlation between TTHM and HAA5 in the third trimester ($r = 0.86$, $p < 0.0001$). An analysis of the trihalomethanes and haloacetic acid constituents showed a moderately strong correlation in the second trimester (bromoacetic acid and chloroacetic acid: $r = 0.66$, bromoacetic acid and dibromochloromethane: $r = 0.60$, and chloroacetic acid and dibromochloromethane: $r = 0.67$) and a strong correlation in the third trimester (dichloroacetic acid and trichloroacetic acid: $r = 0.90$).

For models seeming to show a trend toward an elevated risk associated with a CDBP, we estimated the population attributable fraction for the CDBP exposure as well as for all other predictor variables (prenatal care, marital status, mother's age, tobacco use) included in the model. Generally, all predictors in the model accounted for 15–21 percent of the risk of IUGR. Depending on the model, the population attributable fraction for CDBP exposure varied from

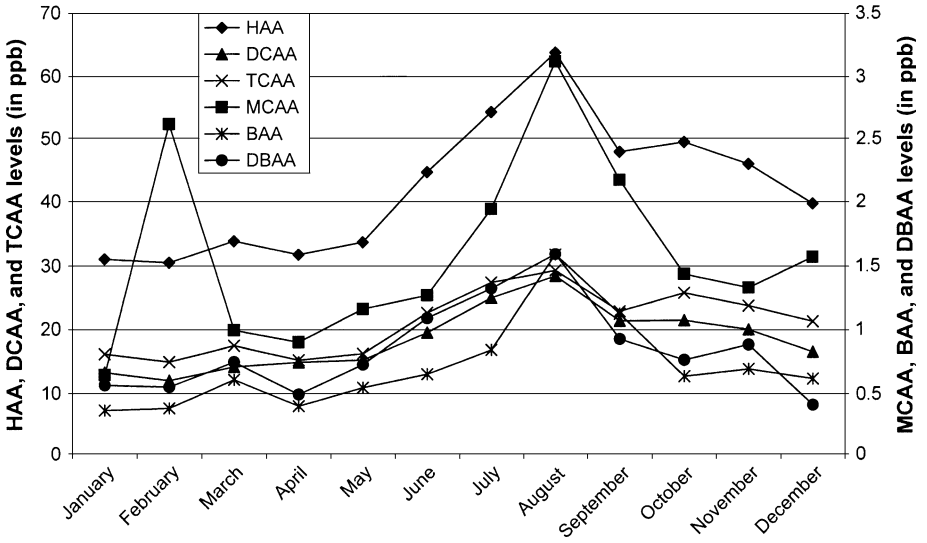

FIGURE 2. Seasonal fluctuation in haloacetic acid (HAA) levels in four regions of a Maryland county, 1997–2002. DCAA, dichloroacetic acid; TCAA, trichloroacetic acid; MCAA, monochloroacetic acid; BAA, bromoacetic acid; DBAA, dibromoacetic acid.

TABLE 2. Mean levels of chlorine disinfection by-products in four regions of a Maryland county, 1997–2002

	Region 1		Region 2		Region 3		Region 4		Total	
	Mean	95% CI*	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
THM levels (ppb)*										
Maximum TTHM*	134		207		129		169		207	
Minimum TTHM	14		24		17		18		14	
TTHM	41.0	35.9, 46.1	70.2	62.4, 78.0	45.6	40.3, 51.0	53.7	47.2, 60.2	52.7	49.3, 56.0
Chloroform	25.0	22.8, 27.2	48.1	44.4, 51.9	28.9	26.4, 31.3	34.4	31.4, 37.3	34.1	32.5, 35.7
BDCM*	11.7	10.6, 12.7	16.1	14.6, 17.6	12.8	11.6, 14.0	13.2	12.0, 14.5	13.4	12.8, 14.1
DBCM*	4.00	3.38, 4.60	5.04	4.29, 5.78	4.27	3.61, 4.93	4.10	3.45, 4.75	4.35	4.01, 4.68
Bromoform	0.27	0.21, 0.33	0.34	0.27, 0.41	0.28	0.21, 0.34	0.27	0.21, 0.33	0.29	0.26, 0.32
HAA5 levels (ppb)*										
Maximum HAA5	68.4		91.7		74.9		90.2		91.7	
Minimum HAA5	12.5		9.4		15.1		21.9		9.4	
HAA5	33.9	31.3, 36.4	52.3	48.9, 55.8	37.9	35.0, 40.7	45.7	42.2, 49.1	42.4	40.7, 44.1
CAA*	1.3	1.0, 1.5	1.9	1.3, 2.5	1.4	1.0, 1.7	1.9	1.4, 2.3	1.6	1.4, 1.8
DCAA*	15.0	13.8, 16.1	22.1	20.3, 23.7	16.4	15.1, 17.7	20.2	18.6, 21.9	18.4	17.7, 19.2
TCAA*	16.4	15.1, 17.7	26.8	25.0, 28.6	18.8	17.4, 20.2	22.2	20.5, 23.8	21.0	20.2, 21.9
BAA*	0.65	0.51, 0.79	0.78	0.65, 0.92	0.65	0.52, 0.79	0.72	0.60, 0.85	0.70	0.63, 0.77
DBAA*	0.75	0.62, 0.88	0.88	0.71, 1.04	0.86	0.68, 1.04	0.86	0.71, 1.01	0.84	0.76, 0.92

* CI, confidence interval; THM, trihalomethane; TTHM, total trihalomethane; BDCM, bromodichloromethane; DBCM, dibromochloromethane; HAA5, five haloacetic acids; CAA, chloroacetic acid; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid; BAA, bromoacetic acid; DBAA, dibromoacetic acid.

1 percent to 5 percent, with confidence limits including zero. The predictor variables of Kessner Index and unmarried status were found to account for 4–6 percent of the population attributable fraction, with confidence intervals greater than zero. Despite tobacco use being associated with the highest odds ratio in all of our models, it accounted for less than 1 percent of the population attributable fraction because of the low prevalence of tobacco use in the study population.

DISCUSSION

We were not able to demonstrate any consistent, statistically significant effect on IUGR associated with any of the CDBPs in this study, nor did we find any indication of a dose-response relation. We did find some potential for a slightly elevated risk of IUGR during the second and third trimesters. Specifically, there was a statistically significant elevated risk of IUGR for those exposed to higher levels of HAA5 in the third trimester and a nonsignificant elevated risk for those exposed to higher levels of TTHM during the same period. Although the third trimester is the most important in terms of fetal weight gain (during which time the fetus quadruples in size) (30), it is hypothesized that insult prior to the third trimester may hamper fetal growth during this important time by interfering with cellular division (which predominately occurs prior to the third trimester) (31, 32). This hypothesis is supported by Wright et al. (22), who found an association between high levels of TTHM in the second trimester and infants who were small for gestational age (OR = 1.13, 95 percent CI: 1.03, 1.24). TTHM constituent analysis showed a nonsignificant increased risk of IUGR with exposure to high levels of bromoform during each trimester and to dibromochloromethane in the second trimester. Analysis of HAA5 constituents demonstrated a statistically significant elevated risk with exposure to bromoacetic acid in the second trimester and a nonsignificant elevated risk with exposure to chloroacetic acid during the same period. Exposure to higher levels of dichloroacetic acid and trichloroacetic acid in the third trimester also showed a nonsignificant elevated risk of IUGR.

In this study, alcohol consumption was not associated with IUGR when evaluated by using the Mantel-Haenszel chi-square test and was subsequently excluded from the final model. Heavy maternal alcohol consumption has previously been reported to be associated with decreased fetal growth; however, the effects of light-to-moderate consumption on fetal growth are not as clear (33, 34). Because of inadequate records, we were unable to quantify alcohol consumption in this study to determine the effects of heavy consumption (compared with light and moderate consumption) on fetal growth.

For measures of exposure (via zip code), outcome, and potential confounders, we relied on birth certificate information. As noted elsewhere, birth certificate data—particularly the fields that are self-reported—can be imprecise, potentially biasing a study's results (35). However, it is assumed that this imprecision would also be nondifferential, which

TABLE 3. Adjusted odds ratios (95% Wald confidence intervals)* for trimester-specific and total gestational exposure to quintiles of TTHM† (*N* = 15,315) in four regions of a Maryland county, 1998–2002

Exposure and quintile	Entire pregnancy		First trimester		Second trimester		Third trimester	
	OR†	95% Wald CI†	OR	95% Wald CI	OR	95% Wald CI	OR	95% Wald CI
TTHM								
1	Reference		Reference		Reference		Reference	
2	1.01	0.83, 1.22	0.87	0.72, 1.06	1.07	0.88, 1.30	1.18	0.97, 1.44
3	1.11	0.92, 1.35	0.99	0.82, 1.19	1.13	0.93, 1.38	1.20	0.99, 1.46
4	0.98	0.81, 1.20	0.94	0.77, 1.14	1.08	0.89, 1.32	1.05	0.86, 1.29
5	0.98	0.81, 1.19	0.87	0.72, 1.05	1.06	0.87, 1.30	1.17	0.96, 1.42
Chloroform								
1	Reference		Reference		Reference		Reference	
2	1.24	1.02, 1.50	0.88	0.73, 1.07	1.16	0.95, 1.40	1.02	0.84, 1.24
3	1.08	0.88, 1.32	1.04	0.86, 1.25	1.02	0.84, 1.24	0.96	0.79, 1.16
4	1.12	0.92, 1.36	1.03	0.85, 1.24	1.04	0.85, 1.26	0.98	0.81, 1.19
5	1.04	0.85, 1.27	0.90	0.74, 1.09	1.08	0.89, 1.32	1.07	0.88, 1.29
Bromoform								
1	Reference		Reference		Reference		Reference	
2	1.32	1.08, 1.60	1.15	0.95, 1.39	1.11	0.91, 1.35	1.14	0.94, 1.38
3	1.21	0.99, 1.48	1.08	0.89, 1.31	1.05	0.86, 1.28	1.00	0.82, 1.23
4	1.10	0.90, 1.35	1.05	0.86, 1.28	1.08	0.89, 1.31	1.20	0.99, 1.46
5	1.16	0.94, 1.41	1.01	0.83, 1.23	1.16	0.95, 1.40	1.01	0.83, 1.23
DBCM†								
1	Reference		Reference		Reference		Reference	
2	0.98	0.81, 1.19	0.92	0.77, 1.12	1.07	0.87, 1.30	0.95	0.79, 1.15
3	0.91	0.75, 1.11	0.87	0.72, 1.05	1.19	0.98, 1.45	0.84	0.69, 1.02
4	0.92	0.75, 1.11	0.90	0.75, 1.09	1.13	0.93, 1.38	0.92	0.76, 1.12
5	0.96	0.79, 1.17	0.85	0.70, 1.04	1.15	0.95, 1.41	0.90	0.74, 1.09
BDCM†								
1	Reference		Reference		Reference		Reference	
2	1.05	0.87, 1.27	1.02	0.84, 1.23	0.99	0.81, 1.21	0.92	0.76, 1.12
3	0.96	0.79, 1.17	0.96	0.79, 1.16	1.09	0.89, 1.32	1.04	0.86, 1.25
4	1.07	0.89, 1.30	1.00	0.83, 1.22	1.09	0.90, 1.32	0.92	0.76, 1.12
5	0.97	0.80, 1.18	0.90	0.74, 1.10	1.11	0.92, 1.35	0.98	0.81, 1.19

* Controlled for Kessner Index, marital status, teen birth, birth at age >35 years, and tobacco use during pregnancy.
† TTHM, total trihalomethane; OR, odds ratio; CI, confidence interval; DBCM, dibromochloromethane; BDCM, bromodichloromethane.

typically biases results toward the null. Additionally, the trihalomethanes and haloacetic acids are not the only by-products of chlorine degradation. Other products, such as haloacetic nitriles and by-products that have yet to be characterized, are frequently found in surface water supplies treated with chlorine, albeit in a much lower concentration than TTHM and HAA5 (14). Therefore, any observed association might not be directly caused by TTHM or HAA5 but instead by other CDBPs. The multicollinear nature of these by-products frequently makes it difficult to discern the most important exposure agent.

Our lack of a consistent significant effect may be due to an actual lack of an effect of CDBPs on IUGR, a problem of exposure misclassification in our study population, or a lack of power in our study sample. Dodds et al. (19) and Jaakola et al. (36) found no effect of CDBPs on measures of IUGR. Dodds et al. discuss the possibility that potential misclassification of CDBP levels (i.e., applying sampling-point levels to all in the area) may have led to an inability to detect any association. These authors also state that if the risk of growth retardation were elevated even at the lowest observed CDBP levels, then a minimal effect would be evident when comparing low with high exposure levels, which would also have prevented us from finding an effect in this study. Jaakola et al. did not find an effect when looking at high-color and low-color chlorinated water. However, they did not measure actual CDBP levels, nor did they adjust for confounders.

TABLE 4. Adjusted odds ratios (95% Wald confidence intervals)* for trimester-specific and total gestational exposure to quintiles of HAA5† ($N = 10,038$) in four regions of a Maryland county, 1998–2002

Exposure and quintile	Entire pregnancy		First trimester		Second trimester		Third trimester	
	OR†	95% Wald CI†	OR	95% Wald CI	OR	95% Wald CI	OR	95% Wald CI
HAA5								
1	Reference		Reference		Reference		Reference	
2	1.08	0.84, 1.38	1.19	0.94, 1.50	1.03	0.81, 1.31	1.29	1.01, 1.66
3	1.23	0.97, 1.55	1.16	0.92, 1.47	0.98	0.77, 1.25	1.41	1.11, 1.81
4	1.10	0.86, 1.40	0.96	0.75, 1.23	1.06	0.83, 1.34	1.15	0.89, 1.49
5	0.94	0.73, 1.20	0.88	0.69, 1.13	0.98	0.77, 1.24	1.34	1.04, 1.71
CAA†								
1	Reference		Reference		Reference		Reference	
2	1.06	0.84, 1.35	1.03	0.81, 1.31	1.03	0.81, 1.32	0.83	0.65, 1.06
3	1.17	0.92, 1.48	1.12	0.88, 1.41	1.27	1.00, 1.61	0.94	0.75, 1.19
4	1.00	0.78, 1.27	1.03	0.81, 1.31	1.11	0.87, 1.42	0.95	0.75, 1.20
5	0.94	0.74, 1.20	0.91	0.71, 1.16	1.10	0.87, 1.40	1.00	0.79, 1.26
DCAA†								
1	Reference		Reference		Reference		Reference	
2	1.13	0.89, 1.45	1.23	0.98, 1.55	1.00	0.79, 1.28	1.14	0.89, 1.46
3	1.23	0.97, 1.56	1.04	0.82, 1.32	1.00	0.78, 1.27	1.29	1.02, 1.64
4	1.14	0.90, 1.46	0.92	0.72, 1.17	1.12	0.88, 1.41	1.06	0.83, 1.37
5	0.96	0.75, 1.24	0.89	0.70, 1.14	0.96	0.75, 1.22	1.27	0.99, 1.61
TCAA†								
1	Reference		Reference		Reference		Reference	
2	1.10	0.86, 1.40	1.01	0.80, 1.28	1.01	0.80, 1.28	1.30	1.01, 1.65
3	1.08	0.85, 1.38	0.96	0.76, 1.23	0.98	0.78, 1.25	1.34	1.05, 1.71
4	1.09	0.85, 1.38	1.00	0.79, 1.27	0.98	0.77, 1.24	1.21	0.94, 1.55
5	0.97	0.76, 1.24	0.83	0.65, 1.06	0.95	0.75, 1.20	1.20	0.94, 1.54
BAA†								
1	Reference		Reference		Reference		Reference	
2	1.13	0.90, 1.43	0.74	0.58, 0.93	1.23	0.96, 1.57	0.87	0.68, 1.10
3	0.98	0.77, 1.24	0.89	0.71, 1.11	1.30	1.02, 1.65	0.97	0.77, 1.23
4	1.11	0.87, 1.40	0.83	0.65, 1.04	1.30	1.02, 1.66	0.95	0.75, 1.21
5	0.92	0.72, 1.18	0.78	0.62, 0.99	1.05	0.82, 1.35	1.07	0.85, 1.35
DBAA†								
1	Reference		Reference		Reference		Reference	
2	0.88	0.70, 1.12	0.83	0.66, 1.04	1.09	0.86, 1.39	0.87	0.68, 1.11
3	0.96	0.76, 1.21	0.90	0.72, 1.13	1.05	0.82, 1.34	0.99	0.78, 1.26
4	0.93	0.73, 1.17	0.78	0.62, 0.98	1.14	0.90, 1.44	1.10	0.87, 1.39
5	0.84	0.66, 1.07	0.74	0.58, 0.94	1.00	0.79, 1.28	1.05	0.83, 1.33

* Controlled for Kessner Index, marital status, teen birth, birth at age >35 years, and tobacco use during pregnancy.

† HAA5, five haloacetic acids; OR, odds ratio; CI, confidence interval; CAA, chloroacetic acid; DCAA, dichloroacetic acid; TCAA, trichloroacetic acid; BAA, bromoacetic acid; DBAA, dibromoacetic acid.

Studies by Kramer et al. (20), Bove et al. (18), Gallagher et al. (21), and Wright et al. (22) all showed a positive association between CDBP exposure and fetal growth restriction, but some of these results should be interpreted with caution. As mentioned previously, Kramer et al. applied exposure levels to births occurring 2 years after the CDBP was measured (during a drought) in an attempt to allow for proper control of potential maternal confounders not available from birth certificate data during previous years. However, doing so may have led to inappropriate estimations of exposure. Bove et al. were unable to evaluate smoking or alcohol consumption as potential confounders.

TABLE 5. Adjusted odds ratios (95% Wald confidence intervals)* for a threshold analysis of CDBPs† showing a pattern of elevated risk for third-trimester exposures in four regions of a Maryland county, 1998–2002

CDBP and cutpoint (ppb)	Adjusted OR†	95% Wald CI†
TTHM†		
70	1.10	0.94, 1.30
75	1.46	0.97, 1.36
80	1.11	0.91, 1.36
85	1.13	0.91, 1.39
Chloroform		
35	1.05	0.93, 1.19
40	1.07	0.94, 1.22
45	1.09	0.94, 1.26
50	1.10	0.93, 1.30
Bromoform		
0.35	1.12	0.93, 1.34
0.45	1.15	0.91, 1.46
0.55	1.11	0.87, 1.41
0.65	1.11	0.87, 1.42
DBCM†		
5	1.17	0.97, 1.41
7	1.15	0.91, 1.46
9	1.13	0.88, 1.46
11	1.18	0.90, 1.46
BAA†		
0.6	1.05	0.90, 1.22
0.7	1.09	0.94, 1.27
0.8	1.09	0.93, 1.28
DBAA†*		
0.7	1.05	0.90, 1.22
0.8	1.11	0.95, 1.29
0.9	1.06	0.90, 1.25
DCAA†		
14	1.23	1.03, 1.48
15	1.23	1.04, 1.45
16	1.12	0.96, 1.31
17	1.03	0.88, 1.20

* Controlled for Kessner Index, marital status, teen birth, birth at age >35 years, and tobacco use during pregnancy.

† CDBPs, chlorine disinfection by-products; OR, odds ratio; CI, confidence interval; TTHM, total trihalomethane; DBCM, dibromochloromethane; BAA, bromoacetic acid; DBAA, dibromoacetic acid; DCAA, dichloroacetic acid.

The study by Gallagher et al. had the potential for selection bias because births for which there were no quarterly trihalomethane concentrations were excluded. Additionally, for exposure data in each of these studies, quarterly measures, at most, were used as a surrogate for CDBP exposure, with some measures occurring only once a year. From figures 1 and 2, it is apparent that such infrequent measures may significantly over- or underestimate potential prenatal exposure.

Like all previous studies evaluating CDBPs and growth retardation, we used a surrogate measure for exposure classification. Single exposure levels were assigned to mothers living in zip codes, which corresponded to the water utility's point measures. No data were collected on actual maternal exposure to CDBPs. Our exposure assignment assumed that the majority of the exposure occurred at the residence as opposed to other locales such as the workplace. Additionally, we assumed that the mother's residence at the time of delivery was the same as that throughout the pregnancy and that the mother drank tap water. It is expected that this method resulted in some exposure misclassification. While this misclassification would likely have been nondifferential, it would have the effect of biasing toward the null, increasing the opportunity for type II error. Ideal assessment of an individual's exposure would include frequent measurements of CDBPs at the tap, as well as a thorough assessment of all domestic water uses including drinking, showering, cooking, and so forth, similar to the methodology used by Swan et al. (37).

The positive findings in this study may have also been the result of chance due to multiple exposure comparisons. By evaluating multiple CDBP exposures during each trimester as well as over the entire pregnancy, we increased our potential for making a type I error. Additionally, the collinearity of the CDBP constituents makes it difficult to determine whether one or all of the constituents are responsible for the observed effects. In such an early phase of environmental epidemiologic research, this type of problem is difficult to avoid, and the results of this study must be evaluated in the context of subsequent studies with more defined exposure hypotheses.

Our sample size was limited by the study period, our inclusion criteria for exposure, and available outcome standards. The use of post hoc power calculations to determine whether a study was underpowered is inappropriate and has been well contested (38–41). Instead, we focused on the confidence intervals for our point estimates, as suggested by Thomas (41). For the majority of our exposures, our confidence intervals included 1, indicating our inability to rule out no effect. However, our confidence intervals also included adjusted odds ratios similar to those reported in previous studies, indicating a potential slightly increased risk of IUGR for infants whose mothers are exposed to high levels of CDBPs.

We were able to account for only 15–21 percent of the risk of IUGR when the primary exposure and predictor variables were included in this model. Although our final model was not built with the intention of explaining all risk factors for IUGR (i.e., we did not overbuild the model), it appeared to fit the data well (Hosmer-Lemeshow goodness-of-fit test, $p > 0.05$ (dependent upon the exposure being modeled)). Of the models showing the highest risk of IUGR because of CDBP exposure, the population attributable fraction due to CDBP exposure was relatively low (1–5 percent), with confidence intervals including zero. However, if this small effect is real,

it is important because even a small effect could potentially have a large impact on a population given the high prevalence of exposures to chlorination by-products. Furthermore, the health effects of IUGR are real and important.

Small-for-gestational-age neonates are at an increased risk of significant morbidity and mortality during the early stages of life. In addition to numerous metabolic abnormalities, such infants are at an increased risk of fetal distress and infections (30). Although infants small for gestational age frequently become equal in size to those born not small for gestational age within the first year of life, they have a significant increased risk of being short as adults (30). Additionally, small-for-gestational-age infants may be more likely to experience impaired glucose tolerance and reduced beta-cell and pancreatic function later in life (30).

Our assessment of population attributable fractions found that risk factors such as marital status and access to adequate prenatal care are important and potentially modifiable, and that they warrant attention to reduce the burden of disease associated with IUGR. Furthermore, although tobacco use was found to have a relatively low population attributable fraction, such use is likely underestimated in self-reported birth data (42), and tobacco use by pregnant women should also be addressed to reduce the risk of IUGR.

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REFERENCES

1. Control of infectious diseases. MMWR Morb Mortal Wkly Rep 1999;48:621–9.
2. Rook JJ. Formation of haloforms during chlorination of natural waters. J Water Treat Exam 1974;23:234–43.
3. Cantor KP. Drinking water and cancer. Cancer Causes Control 1997;8:292–308.
4. Villanueva CM, Fernandez F, Malats N, et al. Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer. J Epidemiol Community Health 2003;57:166–73.
5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some drinking-water disinfectants and contaminants, including arsenic. Monographs on chloramine, chloral and chloral hydrate, dichloroacetic acid, trichloroacetic acid and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone. IARC Monogr Eval Carcinog Risks Hum 2004;84:269–477.
6. US Environmental Protection Agency. National Primary Drinking Water Regulations: disinfections and disinfection byproducts; final rule. Federal Register 1998;63:69390–476.
7. Murray FJ, Schwetz BA, McBride JG, et al. Toxicity of inhaled chloroform in pregnant mice and their offspring. Toxicol Appl Pharmacol 1979;50:515–22.
8. Schwetz BA, Leong BK, Gehring PJ. Embryo- and fetotoxicity of inhaled chloroform in rats. Toxicol Appl Pharmacol 1974; 28:442–51.
9. Ruddick JA, Villeneuve DC, Chu I, et al. A teratological assessment of four trihalomethanes in the rat. J Environ Sci Health B 1983;18:333–49.
10. Thompson DJ, Warner SD, Robinson VB. Teratology studies on orally administered chloroform in the rat and rabbit. Toxicol Appl Pharmacol 1974;29:348–57.
11. Hunter ES 3rd, Rogers EH, Schmid JE, et al. Comparative effects of haloacetic acids in whole embryo culture. Teratology 1996;54:57–64.
12. Graves CG, Matanoski GM, Tardiff RG. Weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products: a critical review. Regul Toxicol Pharmacol 2001;34:103–24.
13. Reif JS, Bachand A, Andersen M. Reproductive and developmental effects of disinfection by-products. Final report. Ottawa, Ontario, Canada: Bureau of Reproductive and Child Health, Health Canada, 2000.
14. World Health Organization. Environmental Health Criteria 216: Disinfectants and disinfectant by-products. United Nations Environment Programme, International Labour Organisation, World Health Organization; International Program on Chemical Safety, 2000. (http://www.inchem.org/documents/ehc/ehc/ehc216.htm).
15. Bull RJ, Krasner SW, Daniel PA, et al. Health effects and occurrence of disinfection by-products. (Study 448). Denver, CO: AWWA Research Foundation and American Water Works Association, 2001.
16. Nieuwenhuijsen MJ, Toledano MB, Elliott P. Uptake of chlorination disinfection by-products; a review and a discussion of its implications for exposure assessment in epidemiological studies. J Expo Anal Environ Epidemiol 2000;10:586–99.
17. Yang CY, Cheng BH, Tsai SS, et al. Association between chlorination of drinking water and adverse pregnancy outcome in Taiwan. Environ Health Perspect 2000;108:765–8.
18. Bove FJ, Fulcomer MC, Klotz JB, et al. Public drinking water contamination and birth outcomes. Am J Epidemiol 1995; 141:850–62.
19. Dodds L, King W, Woolcott C, et al. Trihalomethanes in public water supplies and adverse birth outcomes. Epidemiology 1999;10:233–7.
20. Kramer MD, Lynch CF, Isacson P, et al. The association of waterborne chloroform with intrauterine growth retardation. Epidemiology 1992;3:407–13.
21. Gallagher MD, Nuckols JR, Stallones L, et al. Exposure to trihalomethanes and adverse pregnancy outcomes. Epidemiology 1998;9:484–9.
22. Wright JM, Schwartz J, Dockery DW. Effect of trihalomethane exposure on fetal development. Occup Environ Med 2003; 60:173–80.
23. Arguello MD, Chrisswell CD, Fritz JS, et al. Trihalomethanes in water: a report on the occurrence, seasonal variation in concentrations, and precursors of trihalomethanes. J Am Water Works Assoc 1979;71:504–84.
24. Zhang J, Bowes WA Jr. Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. Obstet Gynecol 1995;86:200–8.
25. Overpeck MD, Hediger ML, Zhang J, et al. Birth weight for gestational age of Mexican American infants born in the United States. Obstet Gynecol 1999;93:943–7.

26. Alexander GR, Kotelchuck M. Quantifying the adequacy of prenatal care: a comparison of indices. Public Health Rep 1996;111:408–18; discussion 419.
27. Lin CC, Santolaya-Forgas J. Current concepts of fetal growth restriction: part I. Causes, classification, and pathophysiology. Obstet Gynecol 1998;92:1044–55.
28. Greenland S, Drescher K. Maximum likelihood estimation of the attributable fraction from logistic models. Biometrics 1993;49:865–72.
29. Symanski E, Savitz DA, Singer PC. Assessing spatial fluctuations, temporal variability, and measurement error in estimated levels of disinfection by-products in tap water: implications for exposure assessment. Occup Environ Med 2004;61:65–72.
30. Diamond FB Jr. Fetal growth programs future health: causes and consequences of intrauterine growth retardation. In: Barness LA, ed. Advances in pediatrics. Vol 48. St. Louis, MO: Mosby, 2001:245–73.
31. Prada JA, Tsang RC. Biological mechanisms of environmentally induced causes of IUGR. Eur J Clin Nutr 1998;52 (suppl 1):S21–7; discussion S27–8.
32. Smith GC. First trimester origins of fetal growth impairment. Semin Perinatol 2004;28:41–50.
33. Lundsberg LS, Bracken MB, Saftlas AF. Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. Ann Epidemiol 1997; 7:498–508.
34. Windham GC, Fenster L, Hopkins B, et al. The association of moderate maternal and paternal alcohol consumption with birthweight and gestational age. Epidemiology 1995;6:591–7.
35. Dobie SA, Baldwin LM, Rosenblatt RA, et al. How well do birth certificates describe the pregnancies they report? The Washington State experience with low-risk pregnancies. Matern Child Health J 1998;2:145–54.
36. Jaakkola JJ, Magnus P, Skrondal A, et al. Foetal growth and duration of gestation relative to water chlorination. Occup Environ Med 2001;58:437–42.
37. Swan SH, Waller K, Hopkins B, et al. A prospective study of spontaneous abortion: relation to amount and source of drinking water consumed in early pregnancy. Epidemiology 1998;9:126–33.
38. Fletcher R, Fletcher SW. Clinical epidemiology: the essentials. 2nd ed. Baltimore, MD: Williams & Williams, 1998:1–246.
39. Greenland S. On sample-size and power calculations for studies using confidence intervals. Am J Epidemiol 1988;128:231–7.
40. Smith AH, Bates MN. Confidence limit analyses should replace power calculations in the interpretation of epidemiologic studies. Epidemiology 1992;3:449–52.
41. Thomas L. Retrospective power analysis. Conservation Biol 1997;11:276–80.
42. Britton GR, Brinthaupt J, Stehle JM, et al. Comparison of self-reported smoking and urinary cotinine levels in a rural pregnant population. J Obstet Gynecol Neonatal Nurs 2004;33: 306–11.